

FIG. 1

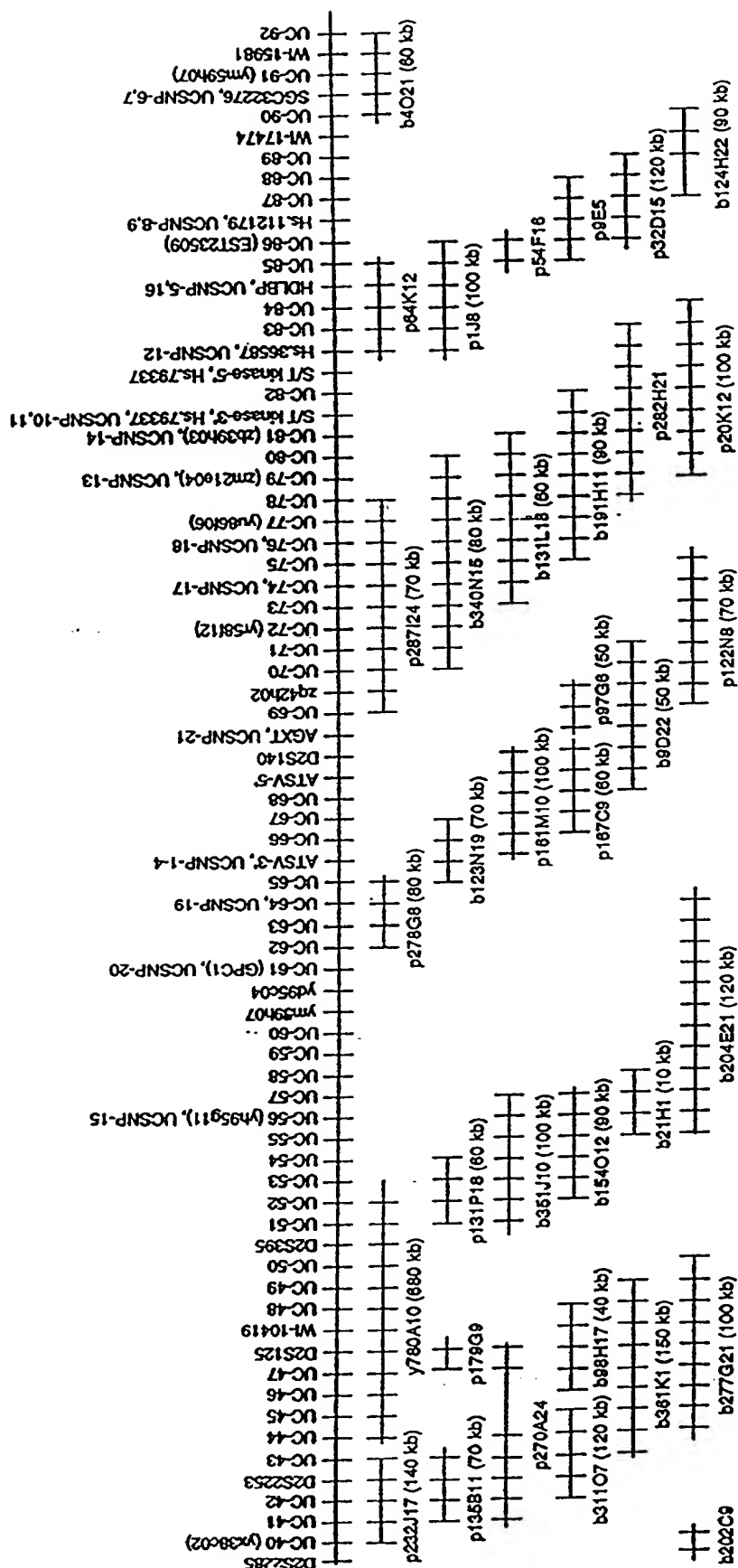


FIG. 2

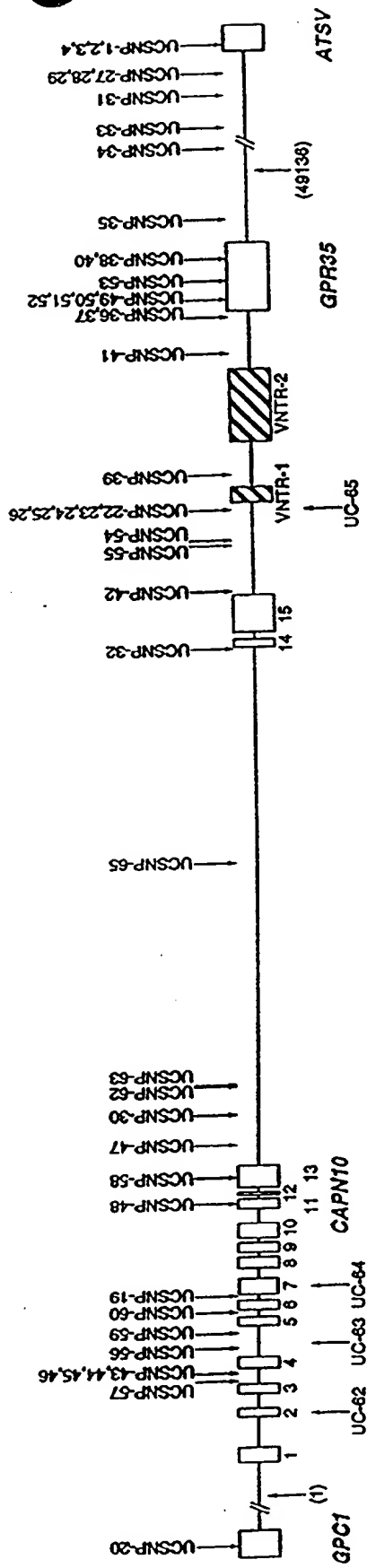


FIG. 3

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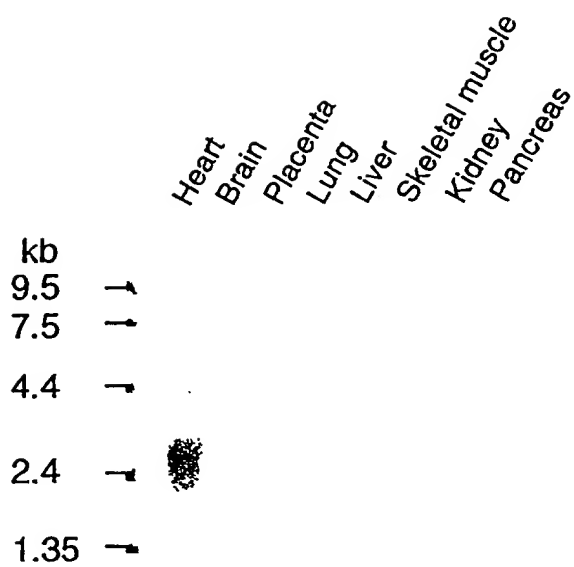


FIG. 4

	Domain I	Domain II
hCAPN5	-----MFSCVKPYEDQNYSLAQDCRRKVLFEPLPATDSDLYY-KGTGPF-----	-----AVRWKRPKGICEDPLRFVDG 67
hCAPN6	-----MGPLKLFKNQYELQKQCKDGRFLCDPTFLPNDSDLFNRLPG-----	-----KVVWKRPPQDISDPLHIVGN 67
hCAPN3	NPTVISASVAPRTAAEPRSPGVPVHPAQSKATEAGCGNPSGIYSAISRNFPIIGVKETFEQLAKKCKLEKVLVYDPEFPDDETSLSFYSGKPF-----	-----IQFVWKRPPPEICENPRFIIDG 115
hCAPN9	MPVLY-----RAPCPQAHVP-----	-----KDARITHSSQSDQDHRQECQLRGTLFEDADFASNSLSFYSERQP-----
hCAPN1	-----HSEELITPVYCTGVSQAQVQKQARELGLG-----	-----RHNALKYLQGYEQQLRVRLQSGTLFDEAFPPVPSLQYKDLGNSSKTYGKIKWRPTELLSNPQPIVGG 101
hCAPN2	-----MAGLAALAKDREAEGLG-----	-----SHERALKYLNQDYALRNECLEAGTLFQDPSPPAIPSAIGFKELGYSYKTRGHRWRPTEICADPQFIIG 91
hCAPN8	-----MAALAAGVSKQRAVAEGLG-----	-----SNQNAVLYLQDQFETLRKQCLNSGVLFKDPFACPSALGKEDLPGSPDQGIWKRPTLCNPFQFIVGG 91
hCAPN10	-----	-----NRAGRGATPARELFDAAPADSSSLFCDLSTPLAQFREDITWRPQECATRLFPDD 59
hCAPN5	ISSHDLHQGGVGNCFVAACSSLASRESLMQKVIPTDKEQENDPRKACAYAGIFHFQWRLG-HVDVVIDERLPTVNNQLTYCHNSRNEFWALVEKAYAKLAGCTYQALDGGNTADALV 186	
hCAPN6	ISNHQLIQGRLLGNKAMISAFSCLAVQESHWTKAIPNHKQDQENDPRKPEKYAGIFHFQWRLG-HVDVVIDERLPTVNNQLTYCHNSRNEFWALVEKAYAKLAGCTYQALDGGNTADALV 187	
hCAPN3	ANRTDICQGGELGDCWFLAAIACLTIANQHLLFRVIP-----HDQSFLENYAGIFHFQWRYGEMVVDVDDCLPTVNNQLVFTKSNNRNEFWALVEKAYAKLAGCTYQALDGGNTADALV 229	
hCAPN9	ATRTDICQGGELGDCWFLAAIACLTIANQHLLFRVIP-----HDQSFLENYAGIFHFQWRYGEMVVDVDDCLPTVNNQLVFTKSNNRNEFWALVEKAYAKLAGCTYQALDGGNTADALV 197	
hCAPN1	ATRTDICQGGELGDCWFLAAIACLTIANQHLLFRVIP-----HDQSFLENYAGIFHFQWRYGEMVVDVDDCLPTVNNQLVFTKSNNRNEFWALVEKAYAKLAGCTYQALDGGNTADALV 215	
hCAPN2	ATRTDICQGGELGDCWFLAAIACLTIANQHLLFRVIP-----HDQSFLENYAGIFHFQWRYGEMVVDVDDCLPTVNNQLVFTKSNNRNEFWALVEKAYAKLAGCTYQALDGGNTADALV 205	
hCAPN8	ATRTDICQGGELGDCWFLAAIACLTIANQHLLFRVIP-----HDQSFLENYAGIFHFQWRYGEMVVDVDDCLPTVNNQLVFTKSNNRNEFWALVEKAYAKLAGCTYQALDGGNTADALV 205	
hCAPN10	PREQGVKQGLLGDWFLCACAAQLKSRLLDQVIP-----PQPSKADQETGRSFTCRINQFGRWVEVITDRLPLCLAGRLCFSRQREDVFWLPLEKXVAKVHGSYEHLMAGQVADALV 175	
hCAPN5	DFTGGVSEPIDLDEGDFANDETRKNQLFERHLKVSROGLISASIKAV-----	-----TAADK-----EARLACGLVKGHAYAVTDV 258
hCAPN6	DFTGTLAEIIDHKGGRYTDLVEEKYKLGELYKTFKGLICCSIESP-----	-----SQEDQ-----EVEDMGLLKGYTYTNTDI 259
hCAPN3	DFTGGVSEPIDLDEGDFANDETRKNQLFERHLKVSROGLISASIKAV-----	-----APSDYKIMKKAJERGLSGCCSIDDGTNTTGTSPSGLNAGELIARHVRNMDNSLLQSDLDPRGSDERPTKTIIPVQYETRAAGLVRGHAYSVTGL 341
hCAPN9	DFTGGVSEPIDLDEGDFANDETRKNQLFERHLKVSROGLISASIKAV-----	-----APSFYELKALRGSLGCFIDT-----ESAAS-----EARTPFGLIKGHAYSVTG 261
hCAPN1	DFTGGVSEPIDLDEGDFANDETRKNQLFERHLKVSROGLISASIKAV-----	-----APSDYKIMKKAJERGLSGCCSIDS-----S-----VLDM-----EATTFKGLVKGHAYSVTGA 279
hCAPN2	DFTGGVSEPIDLDEGDFANDETRKNQLFERHLKVSROGLISASIKAV-----	-----PPNLFKTIQKALQKGLSGCCSIDT-----S-----AADS-----EATTFKGLVKGHAYSVTGA 269
hCAPN8	DFTGGVSEPIDLDEGDFANDETRKNQLFERHLKVSROGLISASIKAV-----	-----PPNLFKTIQKALQKGLSGCCSIDV-----T-----AAEA-----EATTFKGLVKGHAYSVTGA 269
hCAPN10	DFTGGVSEPIDLDEGDFANDETRKNQLFERHLKVSROGLISASIKAV-----	-----VLS-----PRAGARELGEFHAFIVSDL 245
	Domain II	Domain III
hCAPN5	RKVRIGHOLLAPFKSEKLDHRLRNPAGERENGPWSDTSEWQKVSERKQGVTVQDGEFHWTFEDVCRYFTDIKCRVINTSHL-SIHKTWEPEARL-----	-----HGAWTLHEDPRQNRG 373
hCAPN6	RKRLRGERLVEVFSTEKLYHVLRLNPLGRQKSGPWEISEEWQQLTVTDRLNLGLVMSDDGEFHWTFEDVCRYFTDIKCRVINTSHL-SIHKTWEPEARL-----	-----PVFGRKELESV-----VGCWTVDDDPINRST 371
hCAPN3	DEVFP-----KGEKVLRLNPLGRQKSGPWEISEEWQQLTVTDRLNLGLVMSDDGEFHWTFEDVCRYFTDIKCRVINTSHL-SIHKTWEPEARL-----	-----PVRGRKELESV-----VGCWTVDDDPINRST 371
hCAPN9	DQVSF-----RQRIELIRLNPAGEVEMWSDSSPEWRSVGPABQKRLCHTALDGEFHWTFEDVCRYFTDIKCRVINTSHL-SIHKTWEPEARL-----	-----PVRGRKELESV-----VGCWTVDDDPINRST 371
hCAPN1	KQVNY-----RQVVLIRLNPAGEVEMWSDSSPEWRSVGPABQKRLCHTALDGEFHWTFEDVCRYFTDIKCRVINTSHL-SIHKTWEPEARL-----	-----PVRGRKELESV-----VGCWTVDDDPINRST 371
hCAPN2	EEVES-----NGSLQKRLIRLNPAGEVEMWSDSSPEWRSVGPABQKRLCHTALDGEFHWTFEDVCRYFTDIKCRVINTSHL-SIHKTWEPEARL-----	-----PVRGRKELESV-----VGCWTVDDDPINRST 371
hCAPN8	EEVNF-----HGRPEKRLIRLNPAGEVEMWSDSSPEWRSVGPABQKRLCHTALDGEFHWTFEDVCRYFTDIKCRVINTSHL-SIHKTWEPEARL-----	-----PVRGRKELESV-----VGCWTVDDDPINRST 371
hCAPN10	RELQG-----QAGQCTILLRIQNPWGRRCWQGLRREGGEGNSQVDAAVASELSLQ-----	-----EGEFWVEEETLREFDELTVGYTPVTEAGHLQSLYTERLILCHTRALPGAWVK 352
hCAPN5	GGCINHKDTFFQNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
hCAPN6	GGCINNRDTFLNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
hCAPN3	GGCINNRDTFLNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
hCAPN9	GGCINNRDTFLNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
hCAPN1	GGCINNRDTFLNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
hCAPN2	GGCINNRDTFLNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
hCAPN8	GGCINNRDTFLNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
hCAPN10	GGCINNRDTFLNPQYIFEVKPED-----EVLICIQORPKRSTRRGKGENLAIGFDIYKVE-----E-----NRQYRHSI-----QKKAASSYIINSRSVFLRTDQPEGRYVIPT 472	
	Domain III	Domain IV or T
hCAPN5	TFEPGHTEFLLRVTFDVSNCRELRLDEPHPT-----	-----C-----WSSLOGTPQLVTVQVHLGAGLKD----- 530
hCAPN6	MFQHGRTSEFLRLIFSEAPVQLRELTLDPKMS-----	-----C-----WSSLOGTPQLVTVQVHLGAGLKD----- 532
hCAPN3	TFEPHQBGEFLRLVTFSEKRLSEEVNTISVDRPVKKKTKPIIFVSDRANSKELGVQDESEDEGKTSPOKQKSPQPGQSSDQSEDEGQFRIFKQIAGDDEICADELKKVLT 679	-----
hCAPN9	TFEPHQBGEFLRLVTFSEKRLSEEVNTISVDRPVKKKTKPIIFVSDRANSKELGVQDESEDEGKTSPOKQKSPQPGQSSDQSEDEGQFRIFKQIAGDDEICADELKKVLT 679	-----
hCAPN1	TFEPHQBGEFLRLVTFSEKRLSEEVNTISVDRPVKKKTKPIIFVSDRANSKELGVQDESEDEGKTSPOKQKSPQPGQSSDQSEDEGQFRIFKQIAGDDEICADELKKVLT 679	-----
hCAPN2	TFEPHQBGEFLRLVTFSEKRLSEEVNTISVDRPVKKKTKPIIFVSDRANSKELGVQDESEDEGKTSPOKQKSPQPGQSSDQSEDEGQFRIFKQIAGDDEICADELKKVLT 679	-----
hCAPN8	TFEPHQBGEFLRLVTFSEKRLSEEVNTISVDRPVKKKTKPIIFVSDRANSKELGVQDESEDEGKTSPOKQKSPQPGQSSDQSEDEGQFRIFKQIAGDDEICADELKKVLT 679	-----
hCAPN10	TFEPHQBGEFLRLVTFSEKRLSEEVNTISVDRPVKKKTKPIIFVSDRANSKELGVQDESEDEGKTSPOKQKSPQPGQSSDQSEDEGQFRIFKQIAGDDEICADELKKVLT 679	-----
hCAPN5	-----SPTGARSTVIKCEGDQKRSVAVQK-----TSTPETNVEGIFYREKLSQPIITVQVNR-----VLKDEFLQGVHLKADPDLQALATLHLDRNSRQ 618	
hCAPN6	-----ANETVNPYLIKCKGKEEVRSPQKN-----TVHAFIDTQALFYRRITDIPITVQVNR-----KFCDFQGLQVHLKADPDLQALATLHLDRNSRQ 620	
hCAPN3	VVKHKKDLKTHGFTLESCKSHALADTQSGKILQEFHKLAKKIAWKLFKRYDTQSGTINSYEHNRVNDAGFHLANQLYDIITHRYADKRRIDFDFIQCFFVLEGRFRAHF 799	
hCAPN9	VLQKKDKIKFKLSLSCNIIISLADTQSGKILQEFHKLAKKIAWKLFKRYDTQSGTINSYEHNRVNDAGFHLANQLYDIITHRYADKRRIDFDFIQCFFVLEGRFRAHF 668	
hCAPN1	IISKHDLRTNGFSLSCNIIISLADTQSGKILQEFHKLAKKIAWKLFKRYDTQSGTINSYEHNRVNDAGFHLANQLYDIITHRYADKRRIDFDFIQCFFVLEGRFRAHF 692	
hCAPN2	VLAKKDIKSDGFIETCKILVHLDSDGSKILQEFHKLAKKIAWKLFKRYDTQSGTINSYEHNRVNDAGFHLANQLYDIITHRYADKRRIDFDFIQCFFVLEGRFRAHF 679	
hCAPN8	VLAKKDIKSDGFIETCKILVHLDSDGSKILQEFHKLAKKIAWKLFKRYDTQSGTINSYEHNRVNDAGFHLANQLYDIITHRYADKRRIDFDFIQCFFVLEGRFRAHF 682	
hCAPN10	PCFPFSVPEGPGPRCVRITLHQHCRPSD-----TEFPIGFIHFQVPEGGRSQDAPPLLLQEPLLSCVPHRYAQEVSRILCLLPAGTYKVPSTYLPDTEGAVTTIATRDRPSTHSQ 654	
hCAPN5	PSNLPGTVAVHILSSYSIMAV----- 639	
hCAPN6	AKVRQGHISFKVISSDDLTEL----- 641	
hCAPN3	DKDGGCIIKLVLEWQLTHYA----- 821	
hCAPN9	STKQKEPIHILNINEFIHLMNI----- 690	
hCAPN1	DTDLGGVTFDFLKMQLTHYA----- 714	
hCAPN2	DPENTGTIELDLISKLCSVL----- 700	
hCAPN8	DKDQNGIVQLSLAENLCCVLV----- 703	
hCAPN10	ENLQGFQEVSVNAVHKT----- 672	

FIG. 5

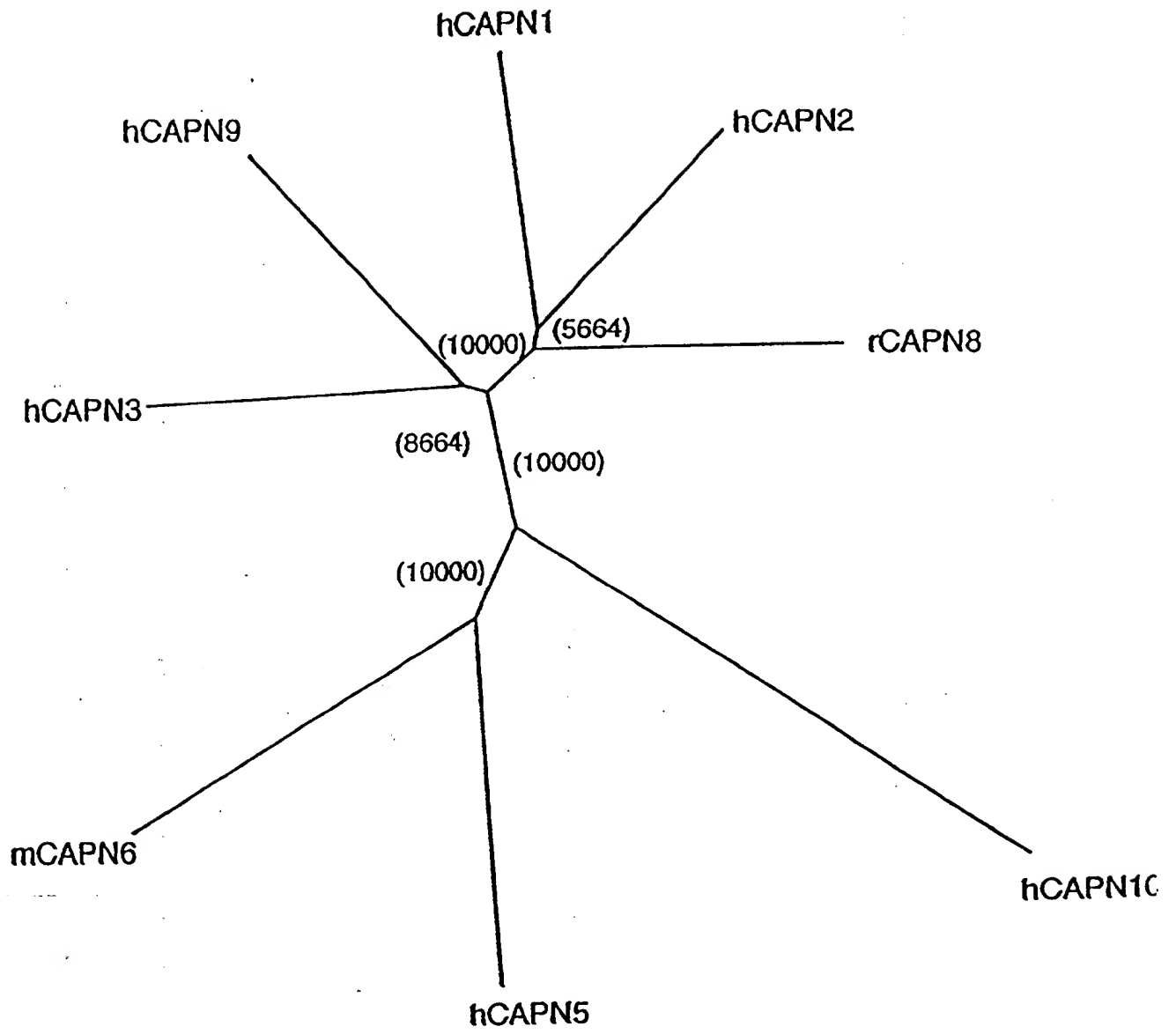


FIG. 6

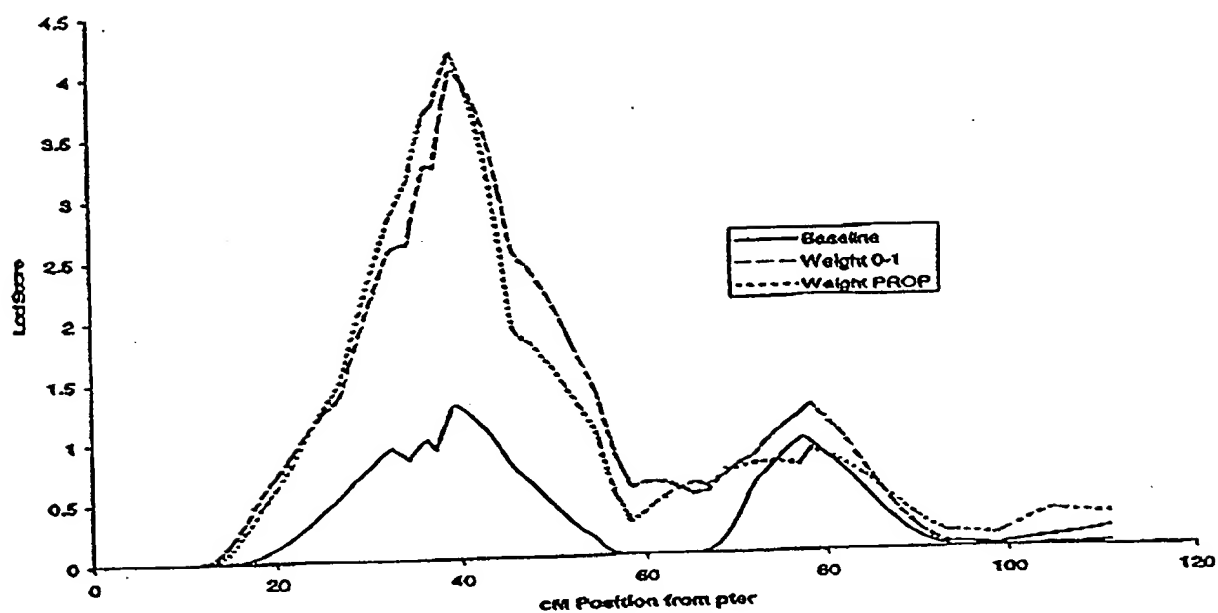


FIG. 7A

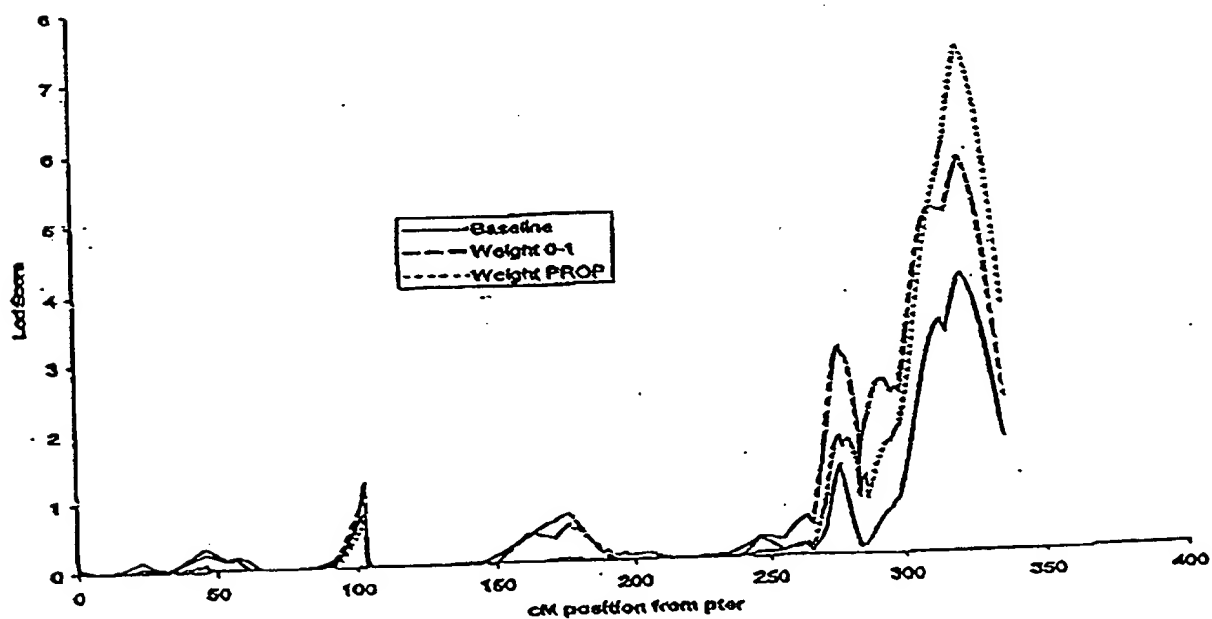


FIG. 7B

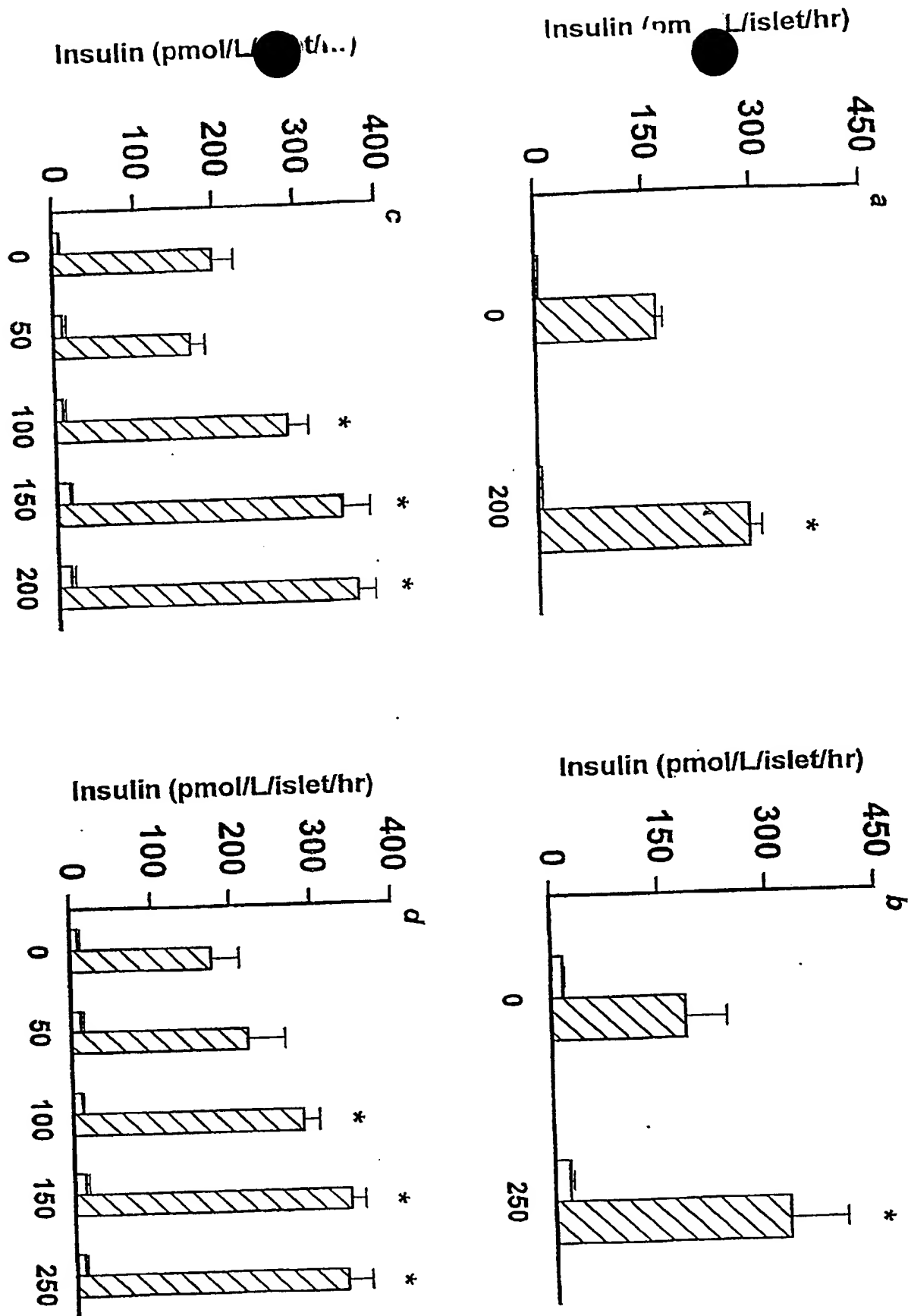


FIG. 8

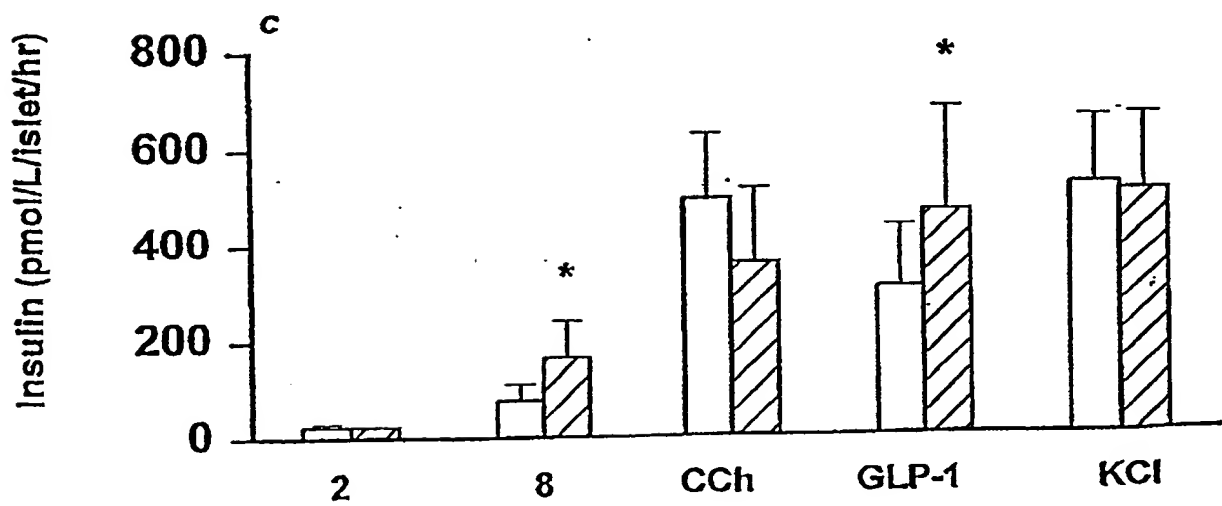
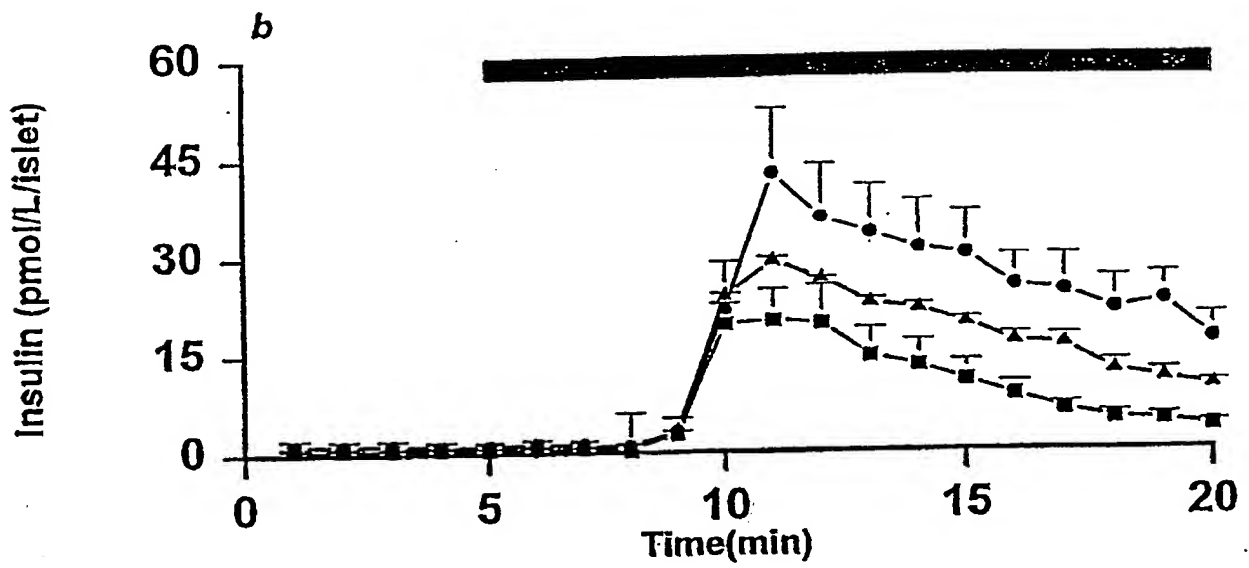
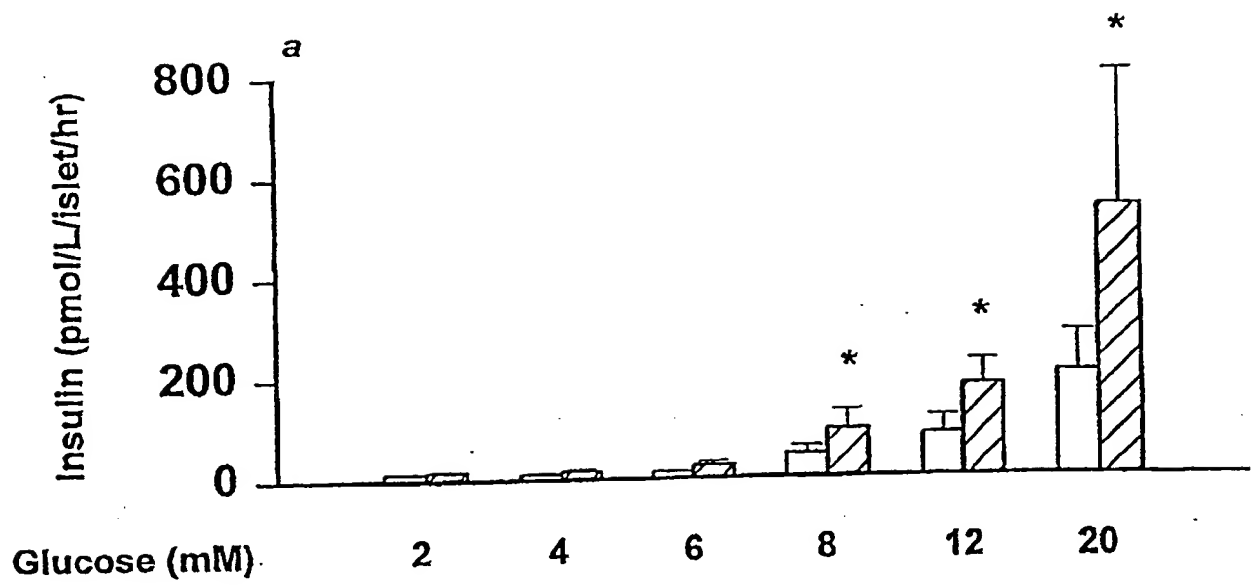


FIG. 9

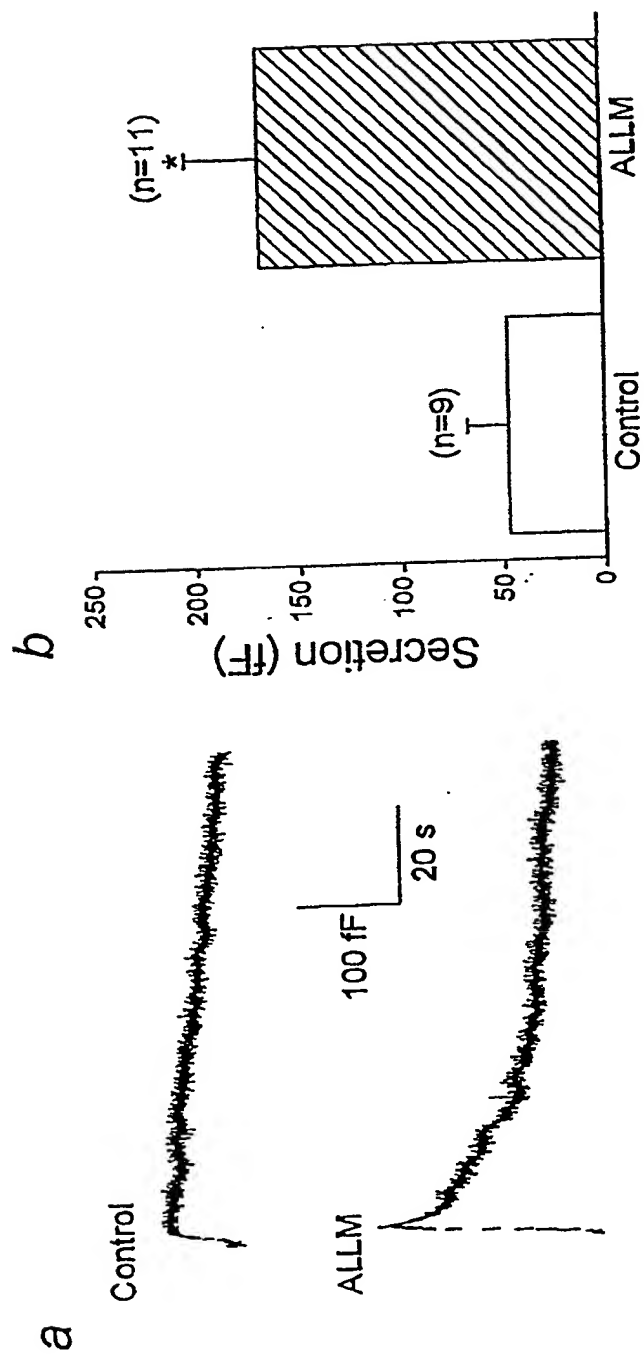


FIG. 10

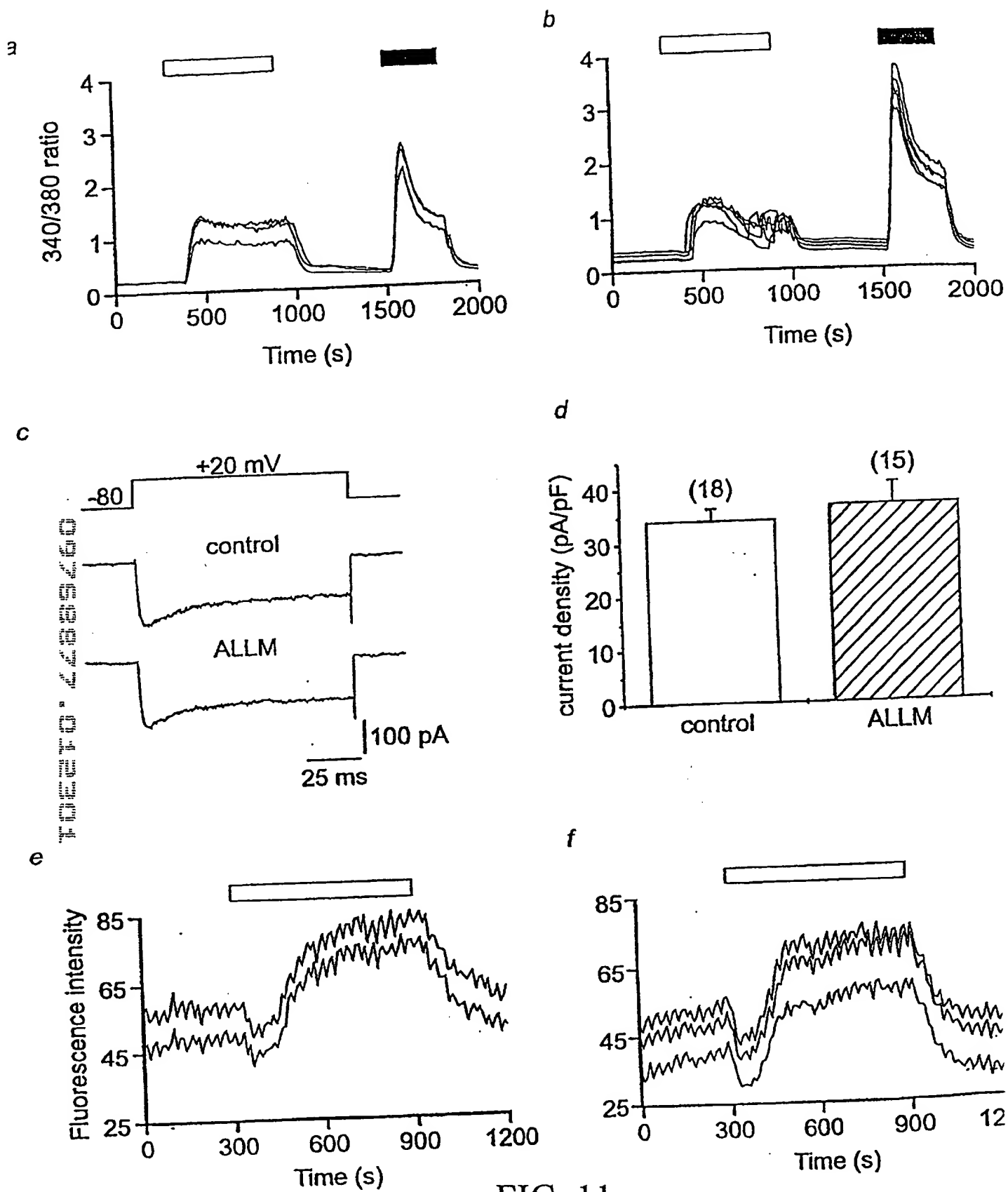


FIG. 11

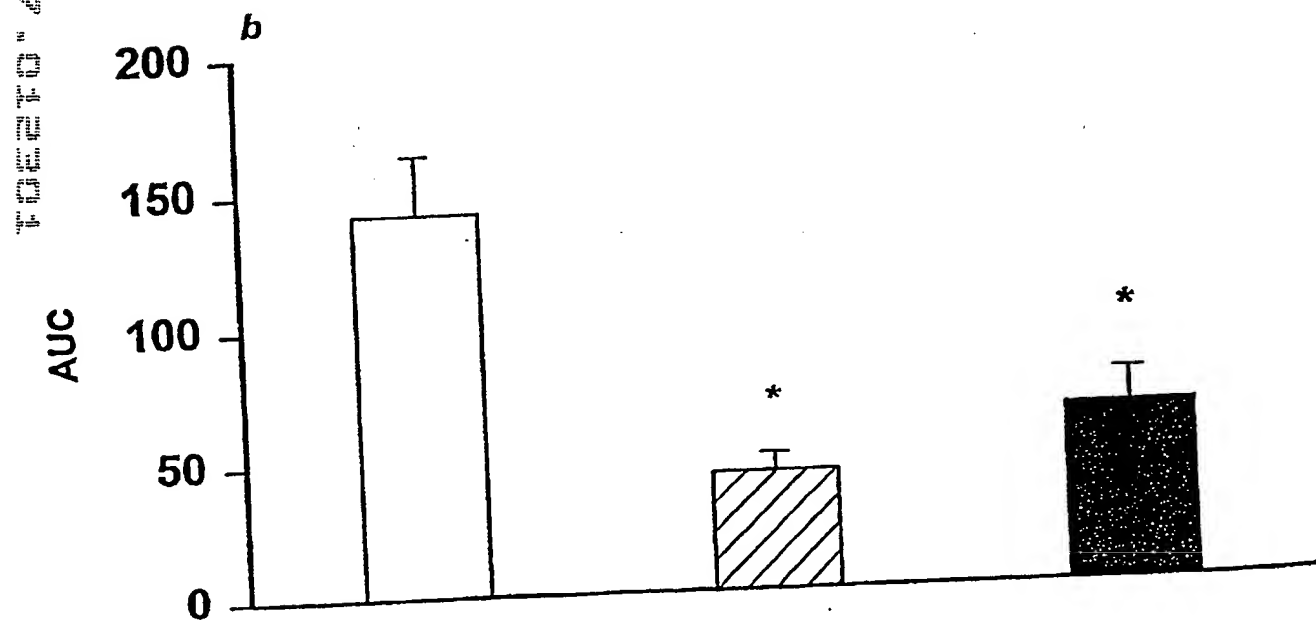
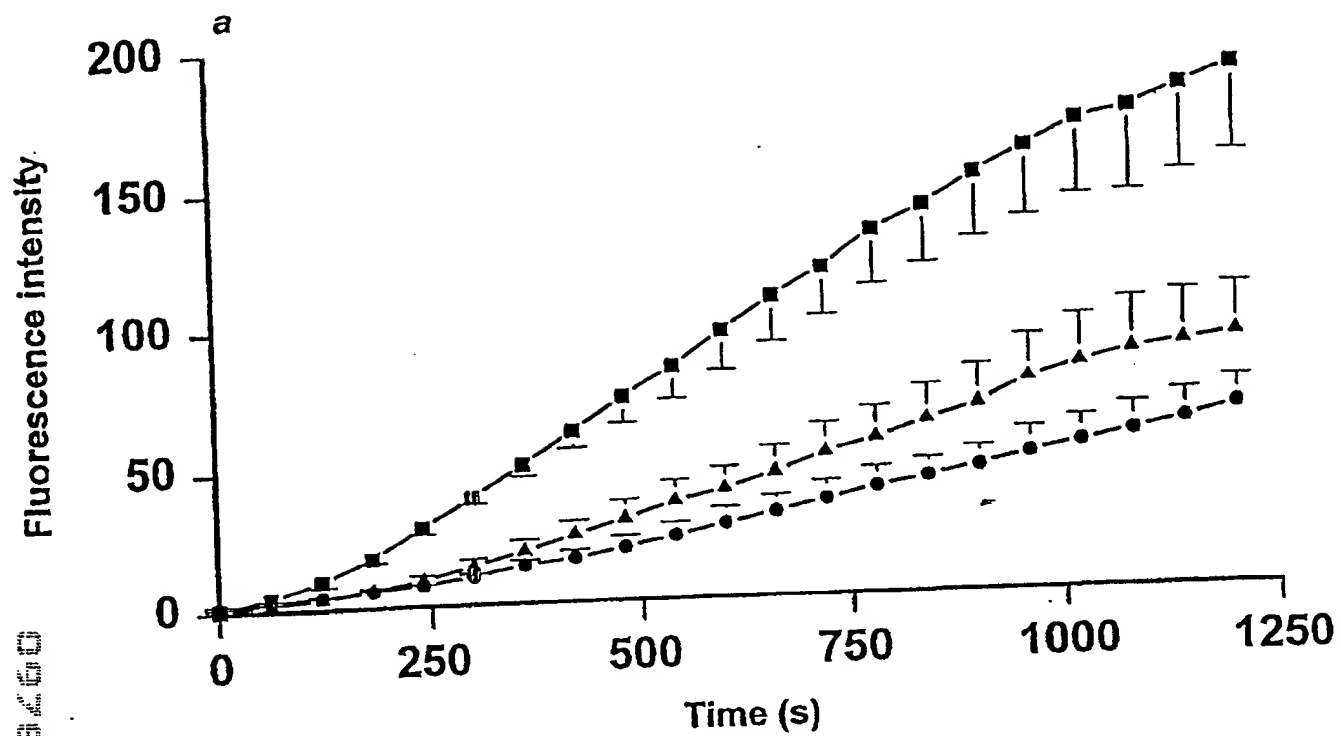


FIG. 12

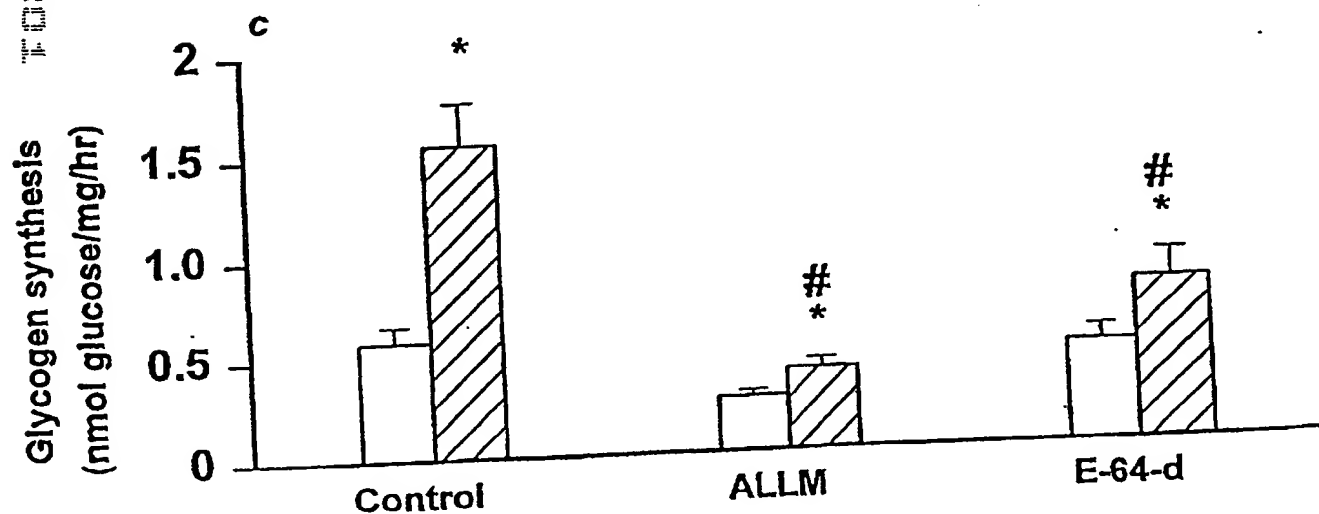
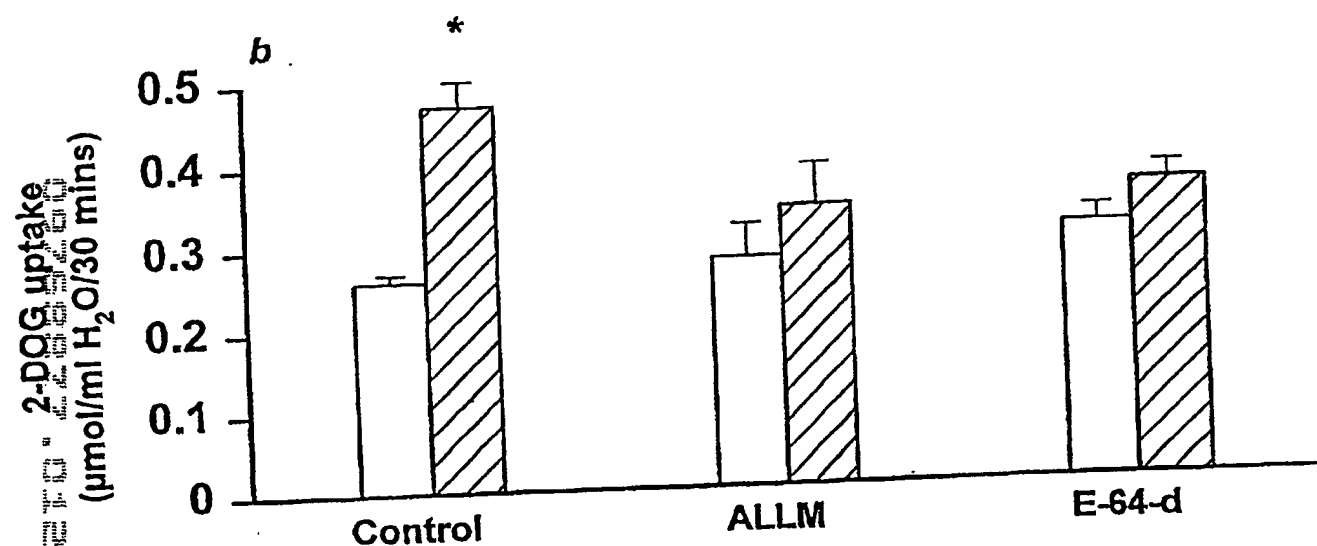
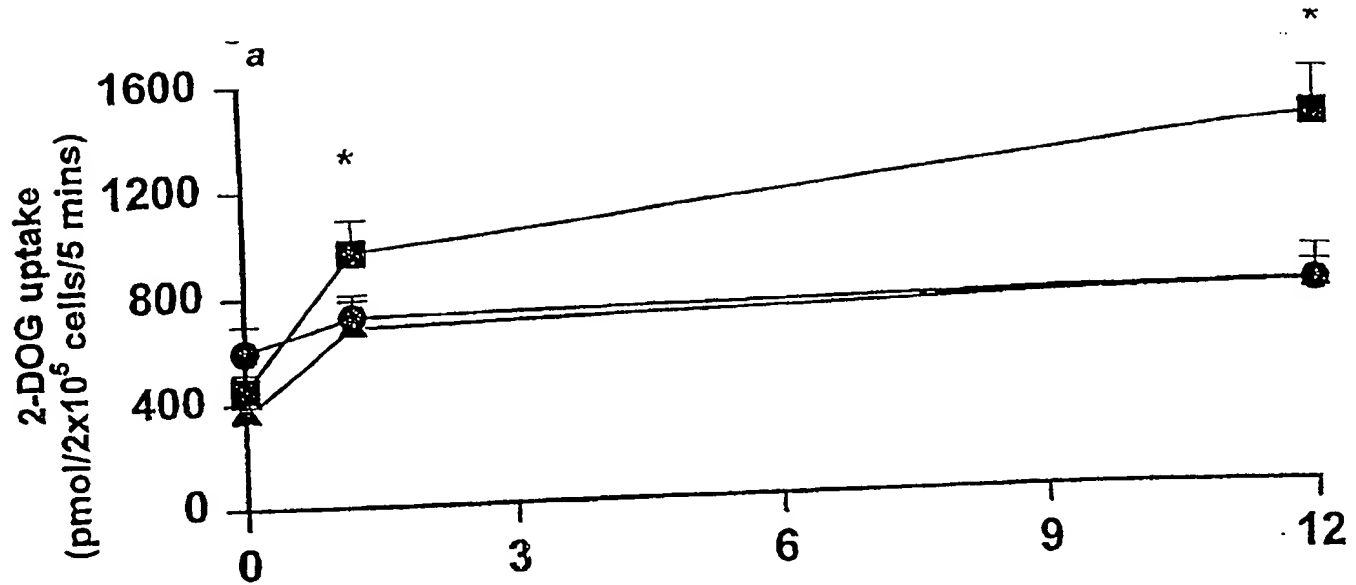


FIG. 13

Fig14. Effect of 48 hours exposure of islets to calpain inhibitors on insulin secretion

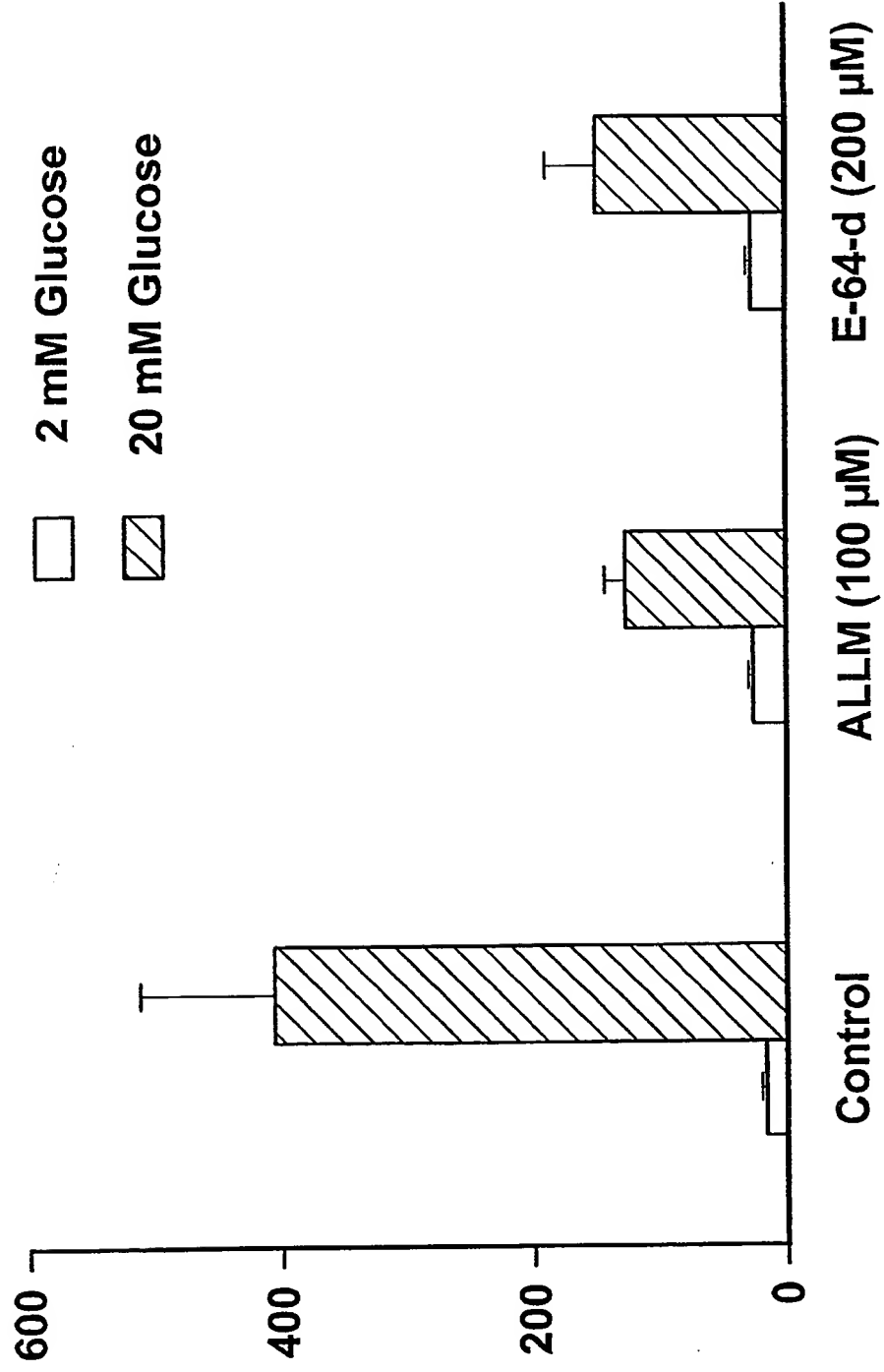


Fig 15 Insulin content in 48 hour cultured islets (n=4)

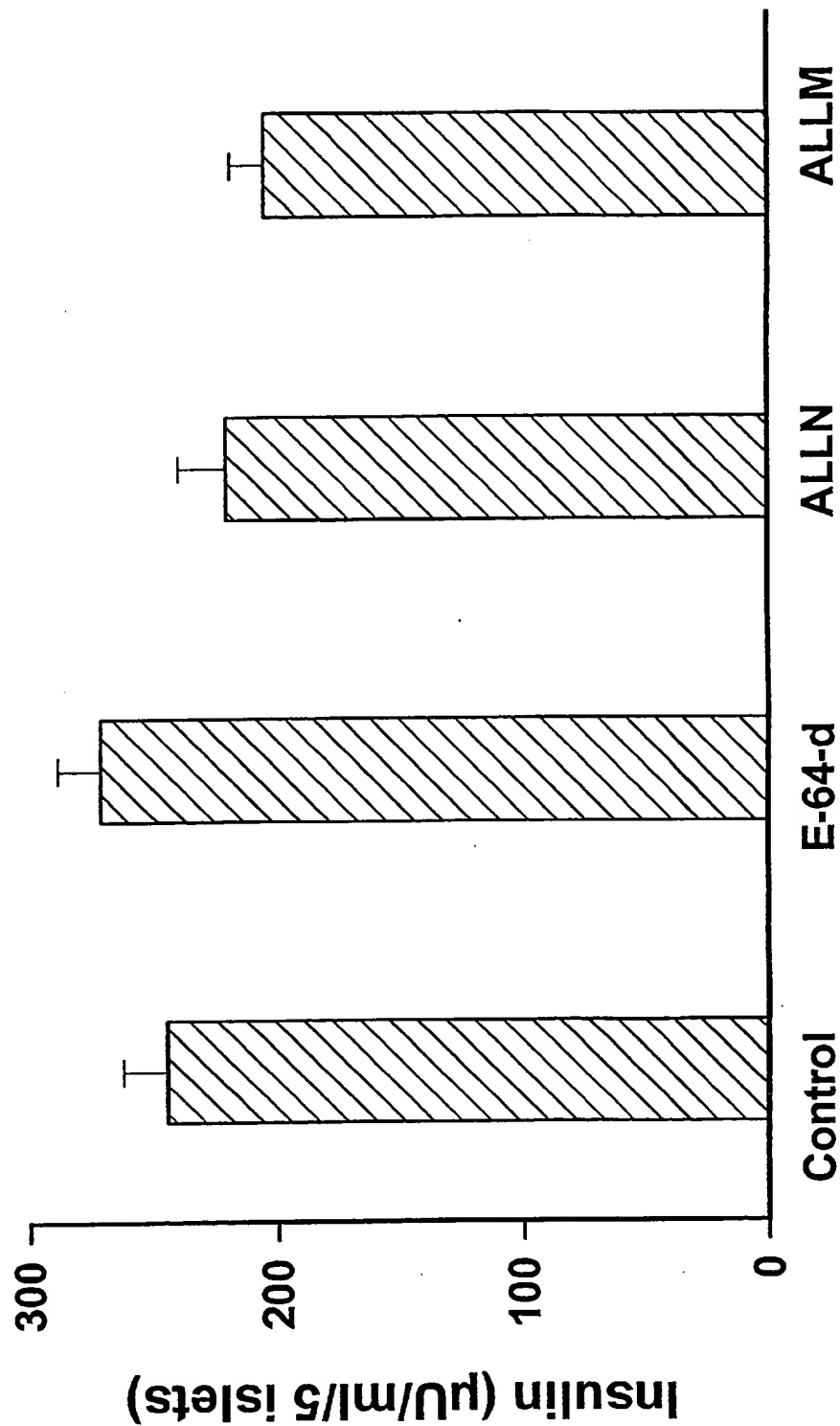


Fig16. ALLM dose response in 48 hour treated islets

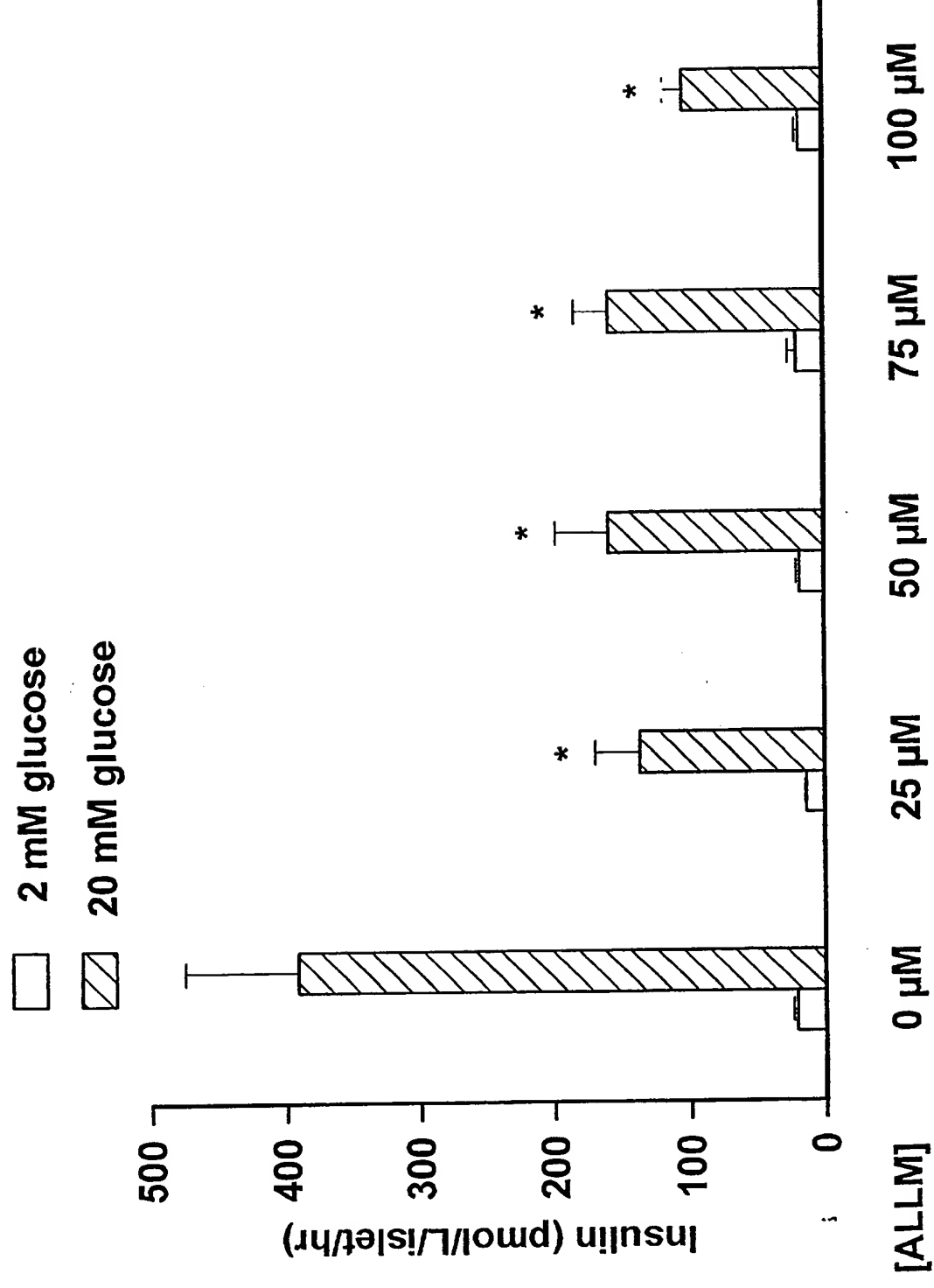
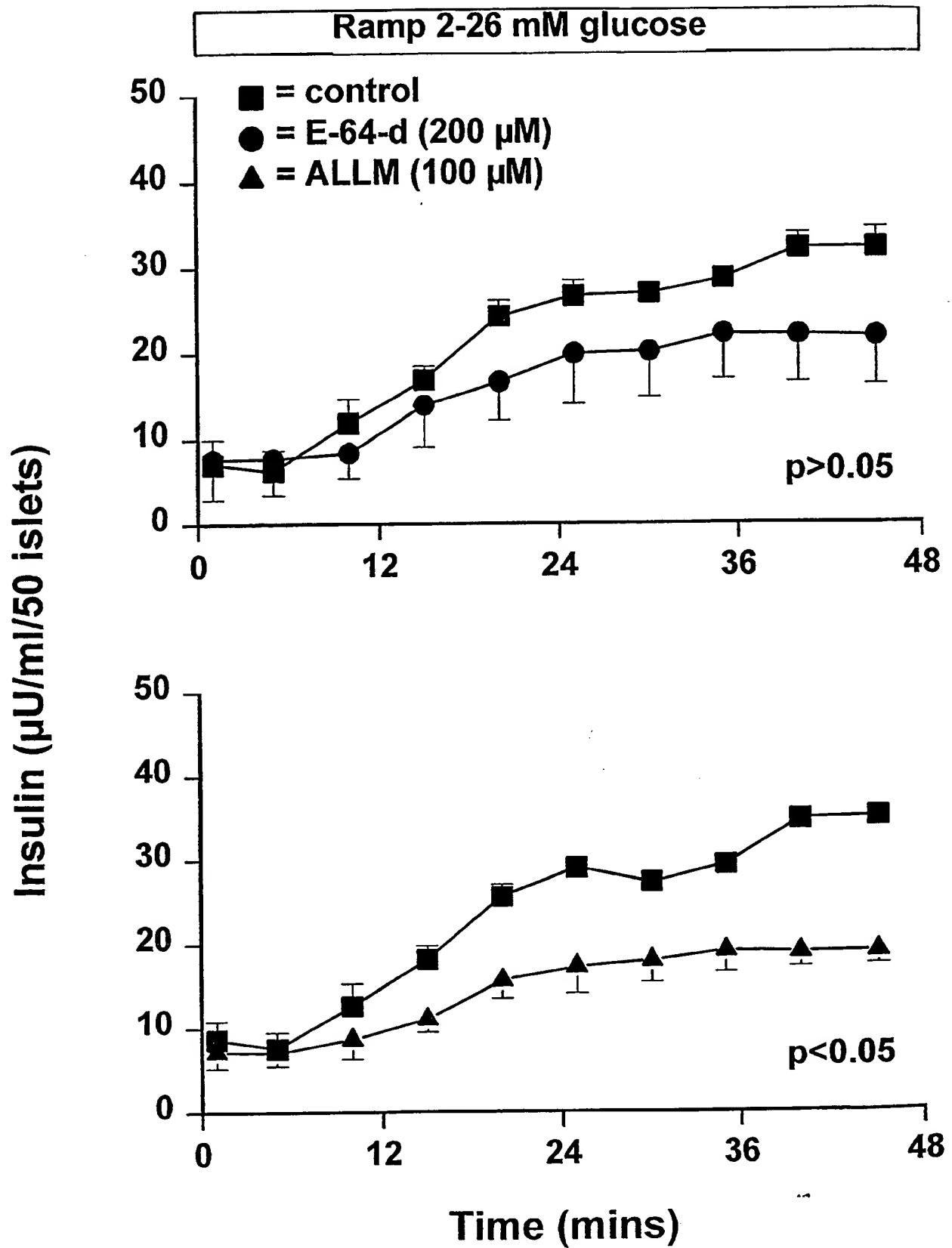


Fig 17. Perifusion of 48 hour cultured islets (n=4)



Insulin secretion in ALLM or E64-d treated mouse islets: Reversal study

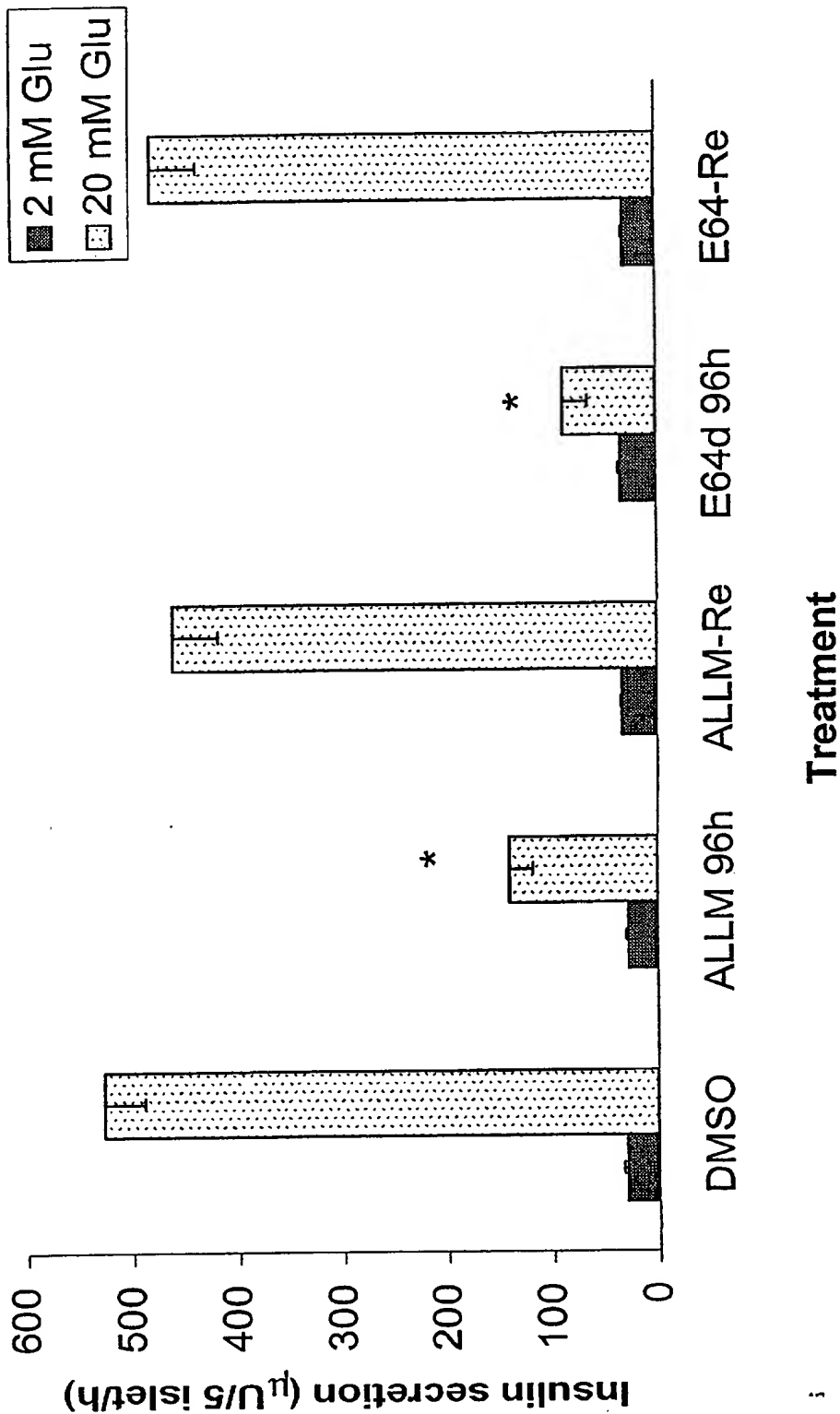


Fig. 18

Fig 19. Insulin secretion by islets following exposure to calpain inhibitors for 48 hrs

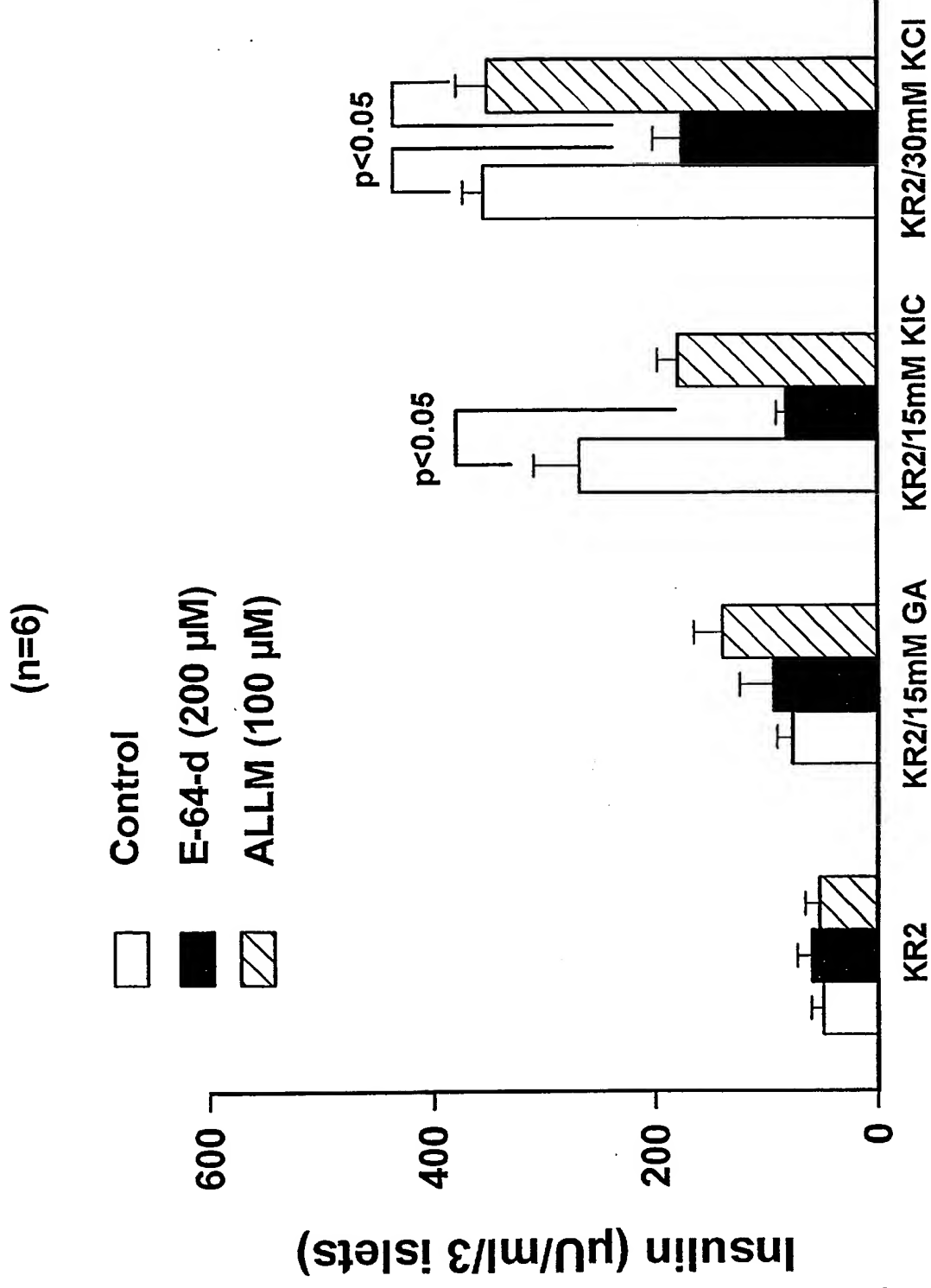


FIG. 20

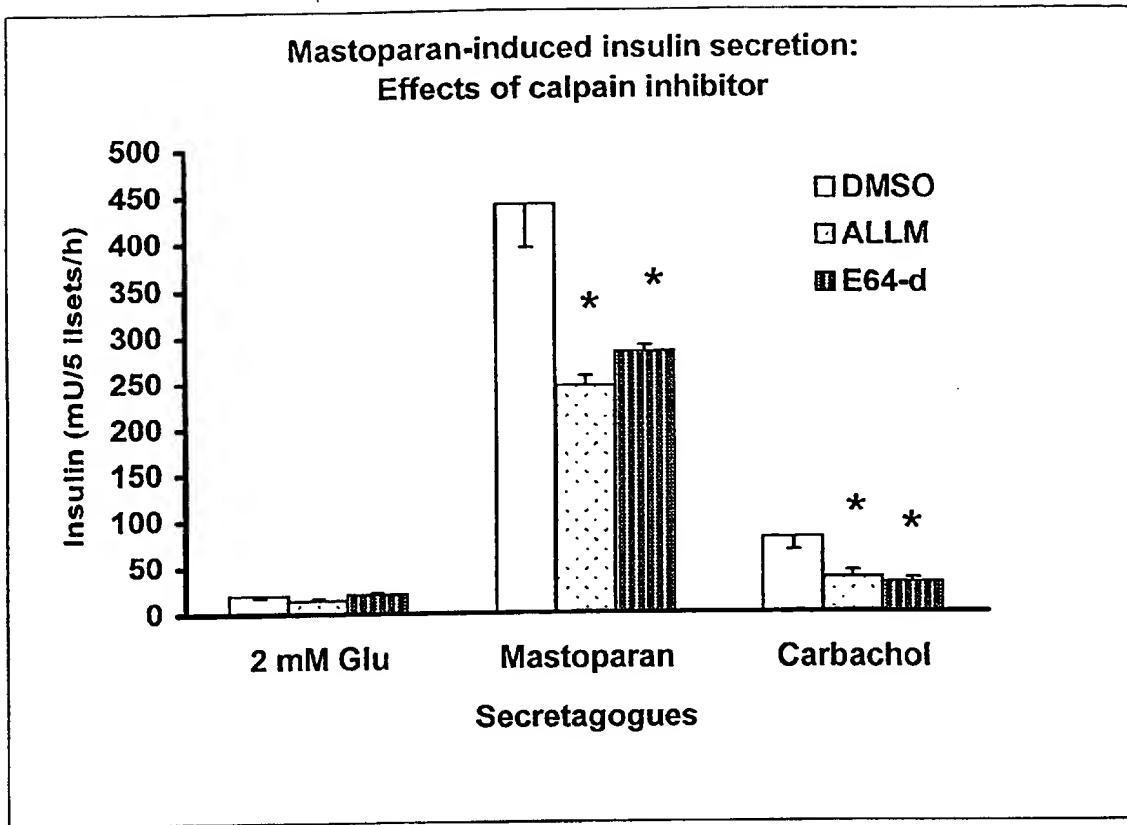
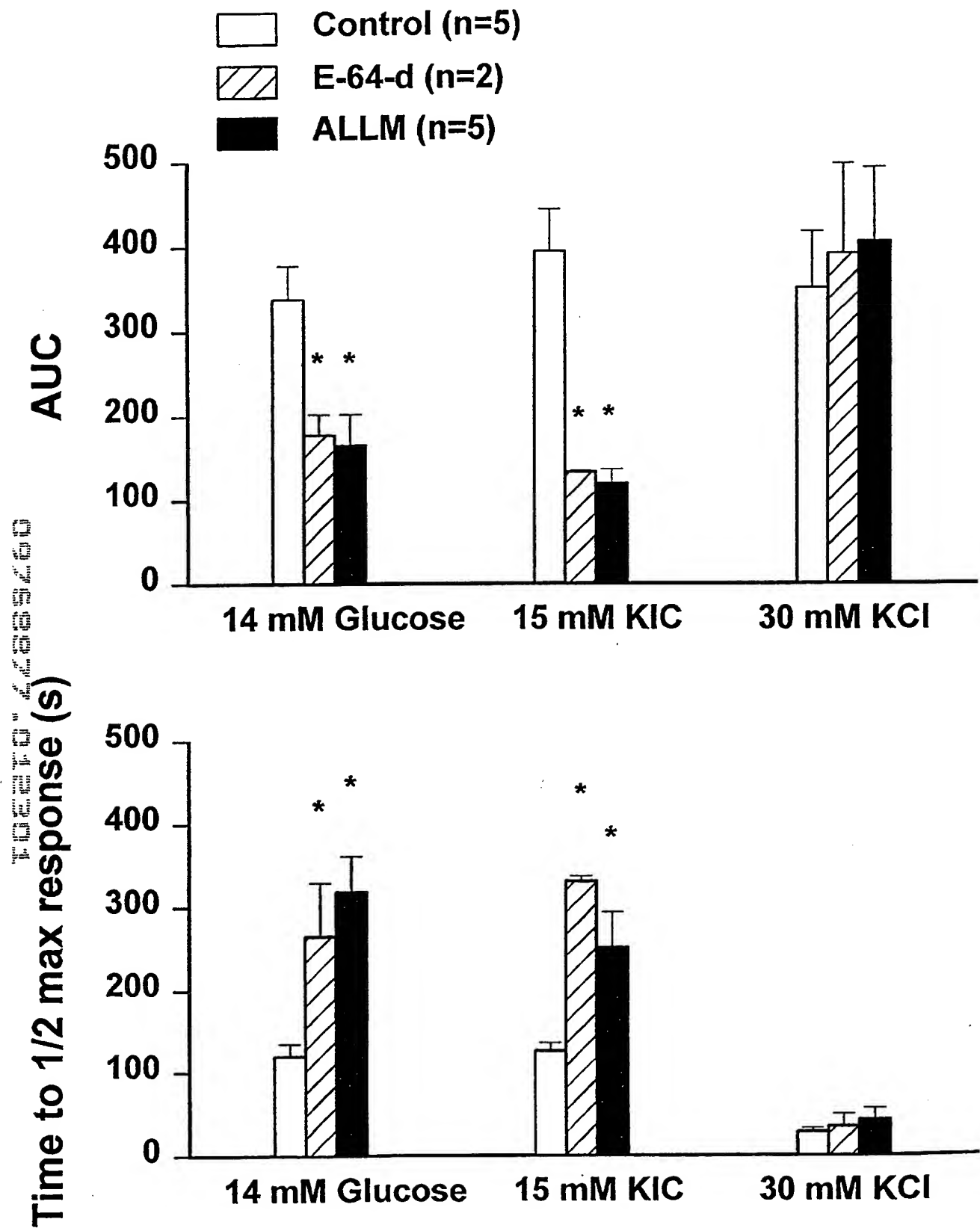


FIG. 20

Fig 21. $[Ca^{2+}]_i$ responses to glucose, KIC and KCl



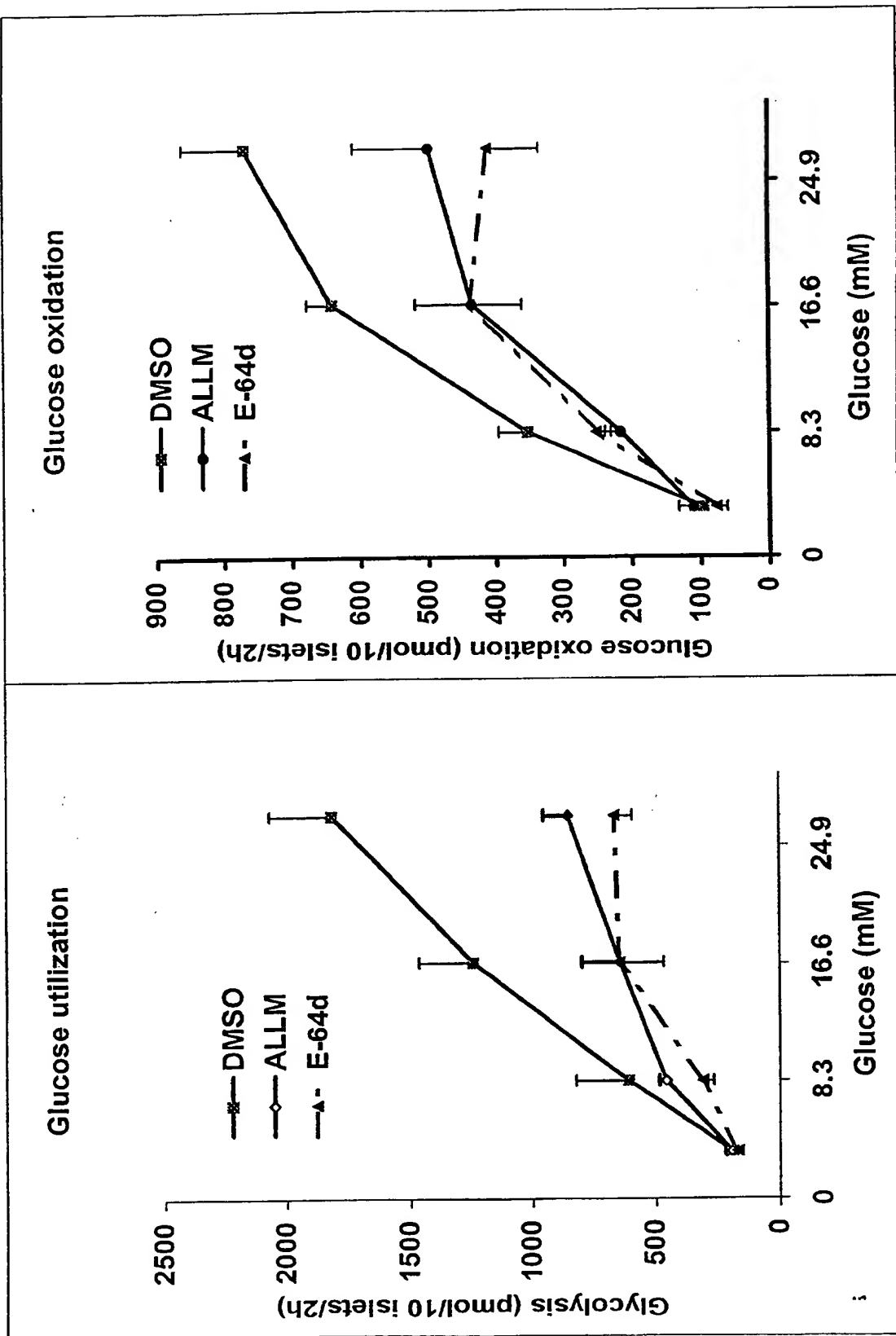
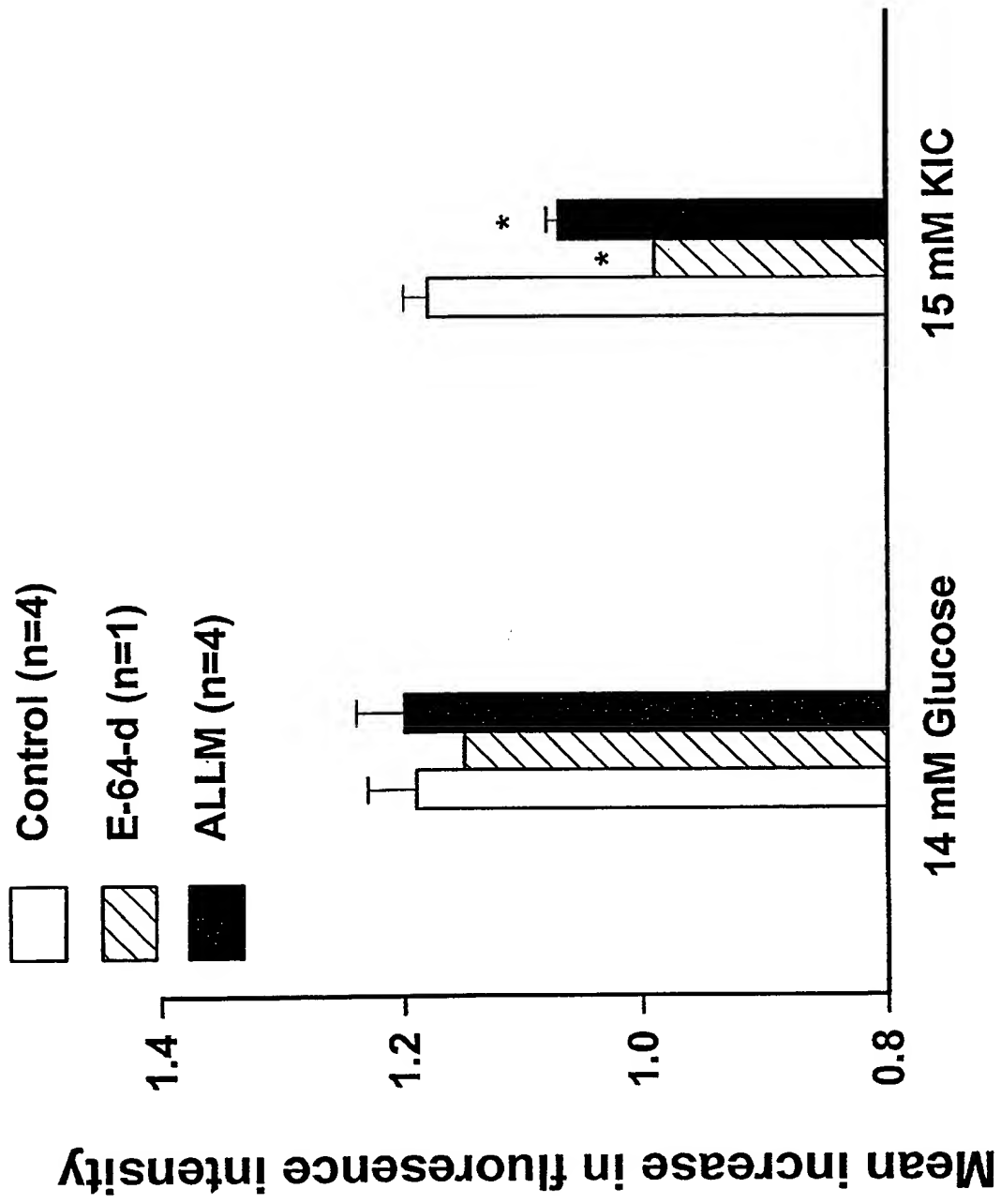


Fig. 22

Fig 23. NAD(P)H responses to glucose and KIC



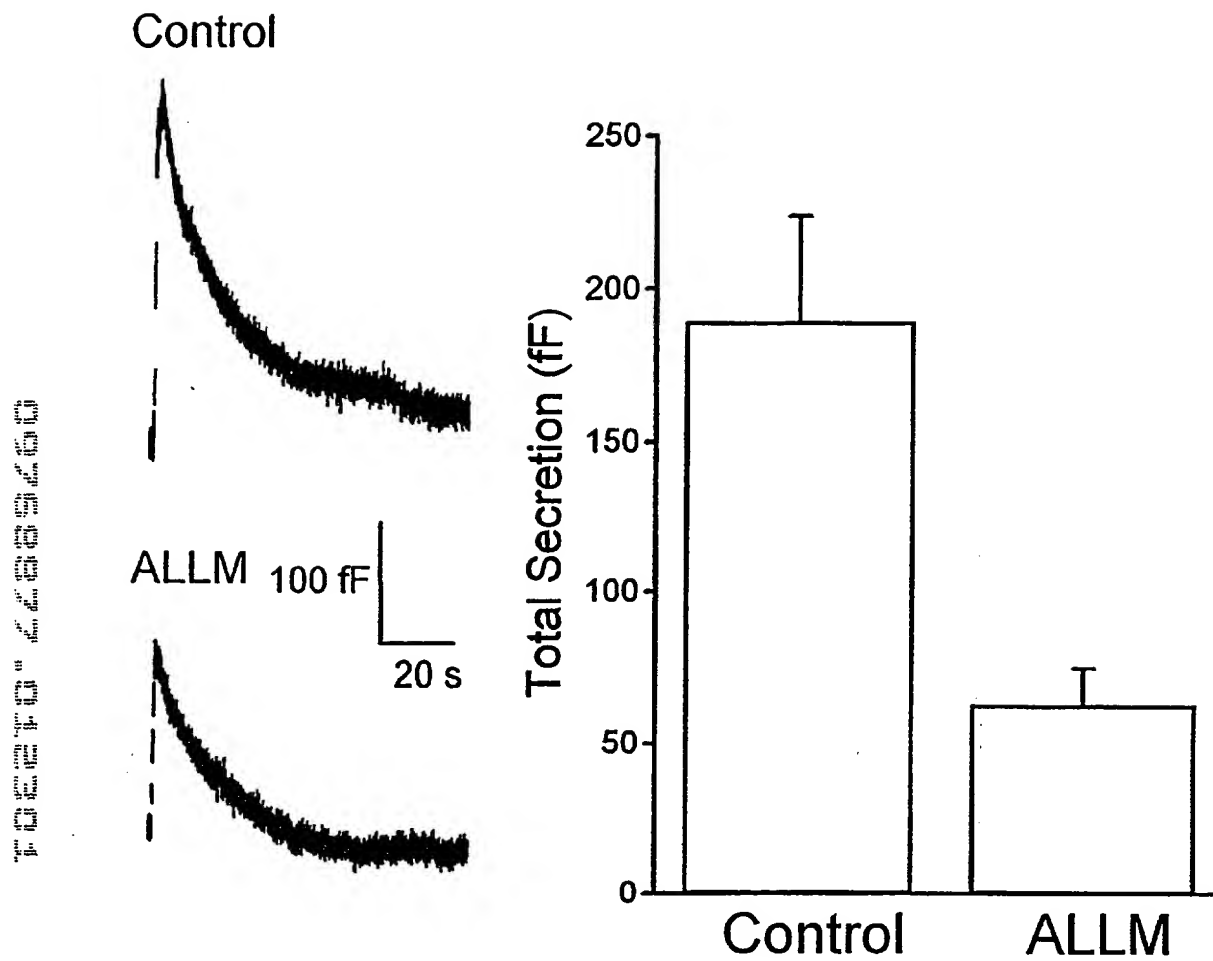
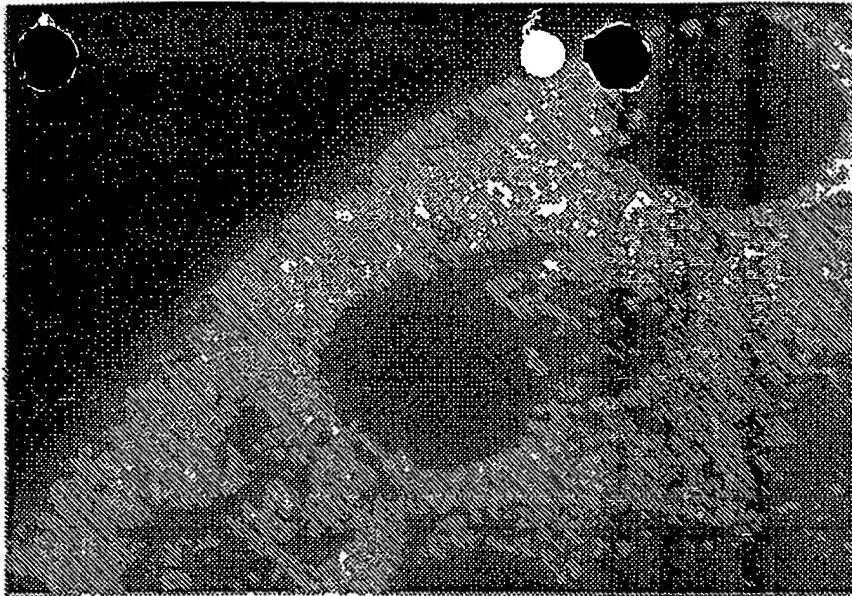
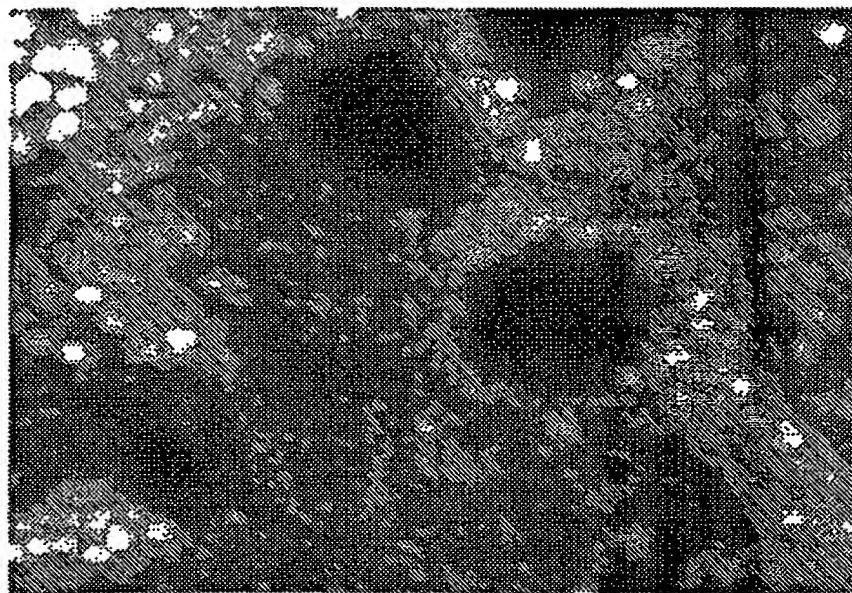


Fig. 24. Measurement of membrane capacitance in isolated β -cells

DMSO



E64d



ALLM

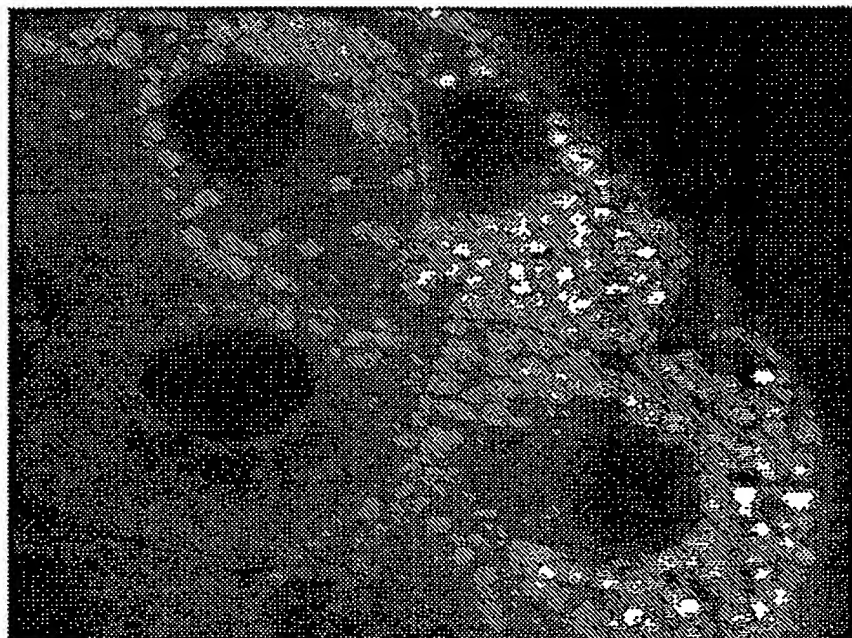


FIG. 25

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"FOOT" 2289260

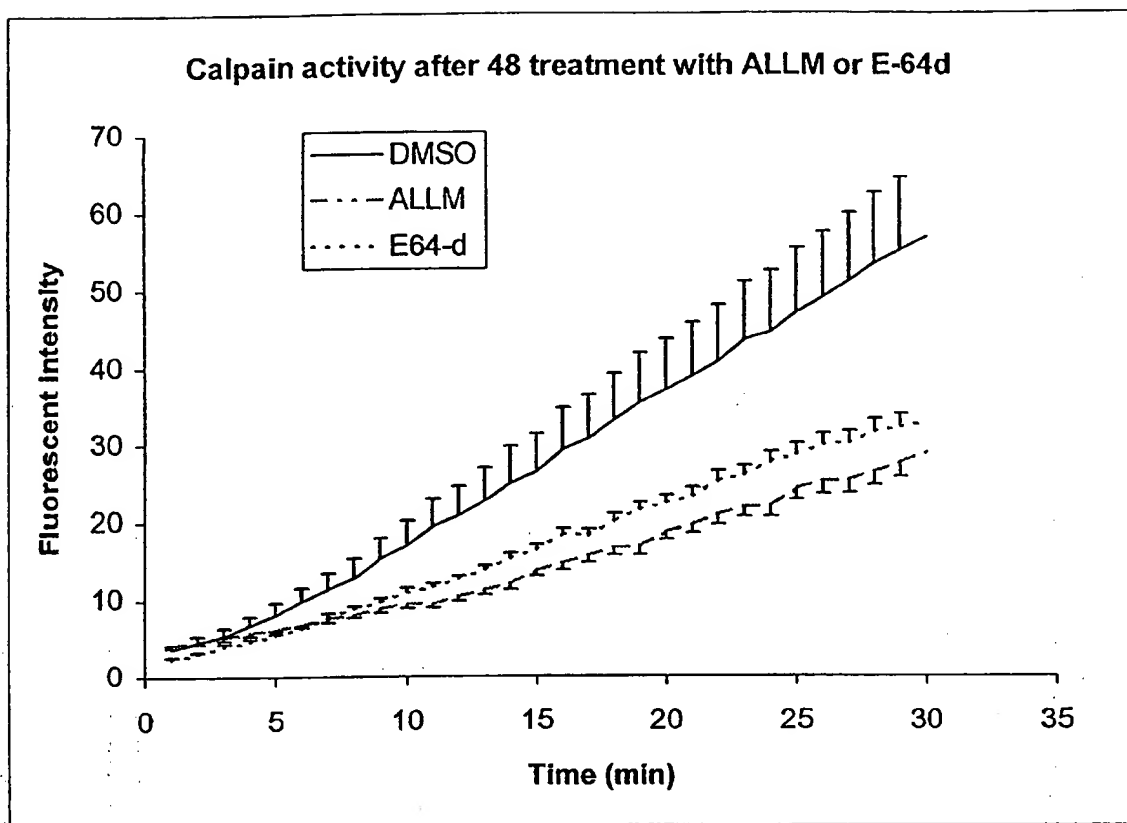


FIG. 26